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Antibiotic Susceptibility of Group A Streptococci: a 6-Year Follow-Up Study

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The susceptibility patterns of group A streptococci over the last 6 years in our hospital were determined. Since our last study, carried out in 1987, all isolates have remained very susceptible in vitro to penicillin and all of the other β-lactam agents tested. We observed resistance to erythromycin, clindamycin, tetracycline, and ofloxacin. The prevalence of erythromycin-resistant group A streptococci did not change appreciably throughout the study period.

Over the last few years there has been an increase in severe group A streptococcus (GAS) infections, including their suppurative and nonsuppurative sequelae (7, 18). Penicillin remains the drug of choice for treatment of GAS infections, and ever since penicillin was first introduced all GAS strains have remained exquisitely sensitive to this antibiotic; despite this, failures of adequate penicillin therapy in the treatment of GAS pharyngitis are being described with increasing frequency (3, 4, 8).

Erythromycin is currently recommended as an alternative antibiotic for treatment of GAS infections in patients allergic to penicillins or in cases of penicillin failure. While in vitro resistance to penicillin has not been described for GAS strains, resistance to erythromycin has been reported. Since 1959, when the first erythromycin-resistant GAS was described by Lowbury and Hurst (9), resistance to this antibiotic has been reported from several countries, with important variations in the resistance rates in different geographic areas; in 1979, Maruyama et al. (10) in Japan reported erythromycin resistance in 61.8% of GAS isolates, and in other parts of the world erythromycin-resistant GAS strains have occasionally been isolated, with resistance rates ranging from 0.7% (13) to 2 to 5% (1, 5, 6, 16, 19, 20). In the last 5 years, an increased incidence has been reported from several centers (14, 15, 17, 21).

In 1987 we studied the susceptibility of 93 GAS isolates from clinical specimens to some commonly prescribed antibiotics (2) and reported the incidence of GAS strains resistant to erythromycin (3.3%), clindamycin (4.3%), and tetracycline (2.2%).

The purpose of the present study was twofold: to ascertain whether the frequency of such resistant strains in our hospital had increased from 1987 to 1992 and also to determine the MICs of some of the newer oral antimicrobial agents against GAS.

A total of 330 GAS strains isolated from clinical specimens between January 1988 and September 1992 in the Hospital Universitario San Carlos, Madrid, Spain, were studied, and the results were compared with those obtained with 93 strains isolated in 1987. Of the 330 GAS strains evaluated, we collected 80 in 1988, 74 in 1989, 76 in 1990, and 100 from January 1991 to September 1992. The sources of the isolates and sites of infection were the upper respiratory tract (75.7%), skin and subcutaneous tissues (8.8%), deep wound infections (8.5%), blood (4.2%), and miscellaneous (2.8%). The antibiotics tested in the previous study were penicillin, erythromycin, clindamycin, tetracycline, vancomycin, and rifampin. In the present study, we also included amoxicillin-clavulanic acid, cefaclor, cefuroxime, roxithromycin, clarithromycin, and ofloxacin. Antimicrobial susceptibility tests were performed by using the same technique as in 1987: a broth microdilution method with serial antibiotic dilutions in Todd-Hewitt broth at concentrations ranging from 0.003 to 16 μg/ml. Microtiter trays were used, and the MICs were read visually. The breakpoints used and the three-category classification scheme (susceptible, intermediately resistant, and resistant) were those recommended by the National Committee for Clinical Laboratory Standards (12). Statistical analysis of data was performed by the chi-square test, with Yates' correction when necessary.

Penicillin remained exquisitely active throughout the study period; the MICs for 90% of the strains were 0.007 μg/ml in 1988 and 1991 to 1992 and 0.015 μg/ml in 1989 and 1990. Our results are similar to those reported by others (5, 20); in 1987 the results obtained (2) were almost identical. Amoxicillin-clavulanic acid displayed unaltered activity against GAS isolates over the study period, with MICs for 90% of isolates ranging from 0.06 μg/ml in 1990 to 0.015 μg/ml in all of the other years. Of the cephalosporins tested, cefaclor was less active than cefuroxime; no resistance to either cefaclor or cefuroxime was shown, and no decrease in susceptibility to either was observed over the study period. The activity of roxithromycin and clarithromycin was comparable to that of erythromycin, and clarithromycin showed slightly more activity than roxithromycin. Table 1 presents the antimicrobial susceptibilities of the GAS strains recovered in our hospital (the isolates from 1987 are also included). In the previous study, done in 1987, we found two strains intermediately resistant to erythromycin (MIC, 2 μg/ml) and one highly resistant (MIC, >64 μg/ml). The frequency of resistance to erythromycin found between 1988 and 1992 has not changed significantly: the percentages of strains intermediately resistant to erythromycin (MIC, 1 to 4 μg/ml) were 3.8% in 1988 and 1 to 2% in the rest of the period studied, and the percentages of strains with MICs of ≥8

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TABLE 1. Resistance rates of GAS strains

Year(s)	No. of strains	% Resistant strains at indicated breakpoint (μg/ml)					
		Erythromycin		Clindamycin		Tetracycline (≥16)	Ofloxacin (≥4)
		1–4	≥8	1–2	≥4		
1987	93	2.2	1.1	3.2	1.1	2.2	Not done
1988	80	3.8	1.2	0.0	2.5	11.2	3.8
1989	74	1.3	2.7	0.0	0.0	8.0	1.3
1990	76	1.3	0.0	1.3	1.3	15.8	3.9
1991–1992	100	2.0	1.0	0.0	2.0	17.0	2.0

μg/ml were 1% in 1988 and 1991 to 1992, 2.7% in 1989, and 0% in 1990.

The frequency of resistance of GAS to clindamycin was 4.3% in 1987, and this decreased to 2.5% in 1988 and to 0% in 1989 (no significant difference); clindamycin resistance rates have remained stable since 1990, with a value of around 2%. Whereas tetracycline resistance was detected in 2.2% of the isolates in 1987, this rate rose significantly ($P < 0.02$) to 11.2% in 1988 and declined to 8% in 1989; in the last years, the incidence of tetracycline-resistant GAS was 17%.

We observed cross-resistance to all of the macrolides tested and to tetracycline, clindamycin, and macrolides in several strains. Of 423 GAS strains isolated from clinical specimens since 1987, 7 were resistant to both erythromycin and clindamycin. One of these was highly resistant to erythromycin, and four strains which were intermediately resistant to erythromycin were also resistant to clindamycin and tetracycline. Vancomycin and rifampin were uniformly active against all isolates, and no resistance was found; the MICs of both antibiotics for 90% of the strains tested (0.5 and 0.06 μg/ml, respectively) remained unchanged over the study years. Ofloxacin was active against GAS (the MIC for 90% of the strains was 1 μg/ml), and no significant changes in susceptibility patterns were observed through the study years.

In this study, we found that GAS strains are still highly susceptible to penicillin and other β-lactam antibiotics, such as amoxicillin-clavulanic acid, cefuroxime, and cefaclor, and no major changes in susceptibility were noted over the years. Vancomycin and rifampin proved uniformly active against the GAS strains tested.

The incidence of erythromycin-resistant GAS isolates in our hospital was low, and there was no increase in their frequency during the 6-year period. These findings are similar to those reported from other parts of Spain (13), from Europe (6, 16), and from the United States (1, 19), although the incidence we found is much lower than that described in Japan (10), Finland (15), or Australia (17). The new macrolides tested did not appear to differ greatly from erythromycin. Some GAS strains were resistant not only to macrolides but also to other antibiotics (clindamycin and tetracycline). We observed a significant increase from 1987 to 1991 and 1992 in the percentage of strains resistant to tetracycline; this is in accordance with several other reports (11, 16). Thus, this antibiotic is not a suitable alternative to penicillin or erythromycin for treatment of GAS infections and therefore its use in children is not recommended.

Erythromycin is the usual choice for treatment of GAS infections in penicillin-allergic patients and is effective against several "new" bacterial respiratory tract pathogens, such as *Legionella* spp., *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. We suggest that increased use of erythromycin has contributed to the appearance of and the continuing increase in resistance to this antibiotic described in several countries (14, 15, 17, 21), although a wide range of geographical variations has been observed.

Although the prevalence of erythromycin-resistant GAS strains reported in our study is low (1.3 to 5%) and has been relatively stable since 1987, the problem has become important in several areas. We therefore emphasize the need to monitor the antibiotic susceptibility of GAS isolates to detect the increasing occurrence of erythromycin resistance.

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